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EXAMINER	
THOMAS, DAVID C	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/766,312	Applicant(s) SCHUSTER ET AL.	
	Examiner David C. Thomas	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 28 February 2007.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 20-34 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 20-34 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed February 28, 2007 is acknowledged. Claims 20-34 (newly added) will be examined on the merits. Claims 1-19 have been canceled.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 20-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerard et al. (U.S. Patent Pub. No. 2002/0081581) in view of Zhao et al. (U.S. Patent No. 6,300,073).

With regard to claims 20, 24, 31 and 32, Gerard teaches a method for amplifying a nucleic acid molecule (see paragraph 2 for overview), said method comprising

incubating an RNA template (such as messenger RNA, paragraph 12, lines 1-5 and 11-21) with a composition comprising (a) a buffer (buffer suitable for amplification, paragraph 11, line 9 and paragraph 193, lines 1-8), (b) two or more proteins having reverse transcriptase (RT) activity (two or more polypeptides with RT activity, paragraph 11, lines 4-7) and (c) at least one DNA polymerase (paragraph 11, line 9 and paragraph 13, lines 15-18);

under conditions which substantially relieve reverse-transcriptase-mediated inhibition of DNA polymerase activity and which are sufficient to amplify a DNA molecule complementary to all or a portion of said RNA template (double-stranded DNA molecule products are produced which are complementary to all or a portion of the nucleic acid templates, also indicating that the DNA polymerase was not substantially inhibited, paragraph 12, lines 6-11),

wherein said DNA polymerase is selected from the group consisting of VENT, DEEPVENT, Tne, Tma, Taq, Pfu and Tth polymerases (preferred DNA polymerases are thermostable and include VENT, DEEPVENT, Tne, Tma, Taq, Pfu and Tth polymerases, paragraph 116, lines 1-11).

With regard to claim 21, Gerard teaches a method for amplifying a nucleic acid molecule wherein said composition comprises:

a first reverse transcriptase enzyme in which the reverse transcriptase activity resides in a single polypeptide (such as the RT from Moloney murine leukemia virus, paragraph 7, lines 1-4 and paragraph 11, lines 17-18); and

a second reverse transcriptase enzyme in which the reverse transcriptase activity resides in a dimeric or multimeric structure (such as the RT from Avian Myeloblastosis Virus, AMV, paragraph 7, lines 23-35 and paragraph 11, lines 20-21).

With regard to claim 22, Gerard teaches a method for amplifying a nucleic acid molecule wherein said first reverse transcriptase enzyme is Moloney murine leukemia virus (M-MLV) reverse transcriptase or a derivative thereof having reduced RNAse H activity (M-MLV H^- RT with reduced or substantially reduced RNase H activity, paragraph 11, lines 14-18) and said second reverse transcriptase enzyme is AMV reverse transcriptase or a derivative thereof having reduced RNAse H activity (AMV H^- RT with reduced or substantially reduced RNase H activity, paragraph 11, lines 14-20).

With regard to claim 23, Gerard teaches a method for amplifying a nucleic acid molecule wherein said composition comprises a first primer and a second primer (one or more primers is used in composition for amplification, paragraph 14, lines 25-27),

wherein said first primer is suitable for facilitating synthesis of first strand cDNA from said RNA template (first nucleic acid molecule is made complementary to RNA template, paragraph 13, lines 6-9), and wherein the combination of said first and said second primer is suitable for amplifying said first strand cDNA (incubating first nucleic acid molecule with composition containing primers and DNA polymerase, column 14, lines 21-27, results in making second nucleic acid molecule and multiple copies of double-stranded molecule, column 13, lines 9-14 and column 14, lines 1-16).

With regard to claim 25, Gerard teaches a method for accurately quantifying a nucleic acid molecule in an essentially sequence-independent manner (double-stranded

products are produced that are complementary to template, which is indicative of accurate quantification of input template nucleic acid, column 14, lines 1-16) comprising

incubating an RNA template (such as messenger RNA, paragraph 12, lines 1-5 and 11-21) with a composition comprising (a) a buffer (buffer suitable for amplification, paragraph 11, line 9 and paragraph 193, lines 1-8), (b) one or more proteins having reverse transcriptase (RT) activity (two or more polypeptides with RT activity, paragraph 11, lines 4-7) and (c) at least one DNA polymerase (paragraph 11, line 9 and paragraph 13, lines 15-18), and (d) a first primer and a second primer (one or more primers is used in composition for amplification, paragraph 14, lines 25-27),

wherein said first primer is suitable for facilitating synthesis of first strand cDNA from said RNA template (first nucleic acid molecule is made complementary to RNA template, paragraph 13, lines 6-9), and wherein the combination of said first and said second primer is suitable for amplifying said first strand cDNA (incubating first nucleic acid molecule with composition containing primers and DNA polymerase, column 14, lines 21-27, results in making second nucleic acid molecule and multiple copies of double-stranded molecule, column 13, lines 9-14 and column 14, lines 1-16),

wherein said incubation is under conditions which substantially relieve reverse-transcriptase-mediated inhibition of DNA polymerase activity and which are sufficient to amplify a DNA molecule complementary to all or a portion of said RNA template (double-stranded DNA molecule products are produced which are complementary to all or a portion of the nucleic acid templates, also indicating that the DNA polymerase was not substantially inhibited, paragraph 12, lines 6-11), and

wherein said DNA polymerase is selected from the group consisting of VENT, DEEPVENT, Tne, Tma, Taq, Pfu and Tth polymerases (preferred DNA polymerases are thermostable and include VENT, DEEPVENT, Tne, Tma, Taq, Pfu and Tth polymerases, paragraph 116, lines 1-11).

With regard to claim 26, Gerard teaches a method for the unbiased quantification of a nucleic acid molecule contained in a sample (such as performing RT reaction at higher temperatures to help reduce mRNA secondary structure and improve specificity of primer binding to reduce background signals, paragraph 135, lines 7-19, in order to produce products complementary to template, paragraph 136, lines 1-8) comprising

incubating an RNA template (such as messenger RNA, paragraph 12, lines 1-5 and 11-21) with a composition comprising (a) a buffer (buffer suitable for amplification, paragraph 11, line 9 and paragraph 193, lines 1-8), (b) one or more proteins having reverse transcriptase (RT) activity (two or more polypeptides with RT activity, paragraph 11, lines 4-7) and (c) at least one DNA polymerase (paragraph 11, line 9 and paragraph 13, lines 15-18), and (d) a first primer and a second primer (one or more primers is used in composition for amplification, paragraph 14, lines 25-27),

wherein said first primer is suitable for facilitating synthesis of first strand cDNA from said RNA template (first nucleic acid molecule is made complementary to RNA template, paragraph 13, lines 6-9), and wherein the combination of said first and said second primer is suitable for amplifying said first strand cDNA (incubating first nucleic acid molecule with composition containing primers and DNA polymerase, column 14,

lines 21-27, results in making second nucleic acid molecule and multiple copies of double-stranded molecule, column 13, lines 9-14 and column 14, lines 1-16),

wherein said incubation is under conditions which substantially relieve reverse-transcriptase-mediated inhibition of DNA polymerase activity and which are sufficient to amplify a DNA molecule complementary to all or a portion of said RNA template (double-stranded DNA molecule products are produced which are complementary to all or a portion of the nucleic acid templates, also indicating that the DNA polymerase was not substantially inhibited, paragraph 12, lines 6-11), and

wherein said DNA polymerase is selected from the group consisting of VENT, DEEPVENT, Tne, Tma, Taq, Pfu and Tth polymerases (preferred DNA polymerases are thermostable and include VENT, DEEPVENT, Tne, Tma, Taq, Pfu and Tth polymerases, paragraph 116, lines 1-11).

With regard to claims 27 and 29, Gerard teaches a method for accurately quantifying a nucleic acid molecule (double-stranded products are produced that are complementary to template, which is indicative of accurate quantification of input template nucleic acid, column 14, lines 1-16) wherein said composition comprises

a first reverse transcriptase enzyme in which the reverse transcriptase activity resides in a single polypeptide (such as the RT from Moloney murine leukemia virus, paragraph 7, lines 1-4 and paragraph 11, lines 17-18); and

a second reverse transcriptase enzyme in which the reverse transcriptase activity resides in a dimeric or multimeric structure (such as the RT from Avian Myeloblastosis Virus, AMV, paragraph 7, lines 23-35 and paragraph 11, lines 20-21).

With regard to claims 28 and 30, Gerard teaches a method for accurately quantifying a nucleic acid molecule wherein said first reverse transcriptase enzyme is Moloney murine leukemia virus (M-MLV) reverse transcriptase or a derivative thereof having reduced RNAse H activity (M-MLV H^- RT with reduced or substantially reduced RNase H activity, paragraph 11, lines 14-18) and said second reverse transcriptase enzyme is AMV reverse transcriptase or a derivative thereof having reduced RNAse H activity (AMV H^- RT with reduced or substantially reduced RNase H activity, paragraph 11, lines 14-20).

With regard to claim 34, Gerard teaches a method for amplifying a nucleic acid molecule wherein said buffer further comprises a sulfur-containing compound and a potassium-containing compound (buffer for synthesis of cDNA molecule may include sulfate forms of TRIS buffer, as well as potassium chloride or acetate paragraph 121, lines 1-13, and also dithiotreitol, paragraph 193, lines 1-8).

Gerard does not teach a method for amplifying a nucleic acid molecule wherein said buffer comprises an effective amount of at least one glutamate-containing compound, wherein the total glutamate concentration is about 1 mM to about 500 mM, and wherein said at least one glutamate compound is selected from the group consisting of glutamate salts of organic bases, alkali metal glutamate salts and alkaline earth metal glutamate salts.

Zhao teaches a method of one step RT-PCR using mixes containing a reverse transcriptase such as an RNase mutant version of M-MLV and a thermostable DNA polymerase (column 2, lines 17-24 and column 4, lines 51-58, and a buffer containing

the alkali metal glutamate salt, potassium glutamate, at a concentration resulting in a conductivity in the range of 500 to 20,000 microohms, column 6, lines 18-28).

Zhao does not teach methods of combining multiple reverse transcriptases in a one-step RT-PCR assay, such as M-MLV or AMV reverse transcriptases that are reduced in RNase H activity.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Gerard for performing a one-step RT-PCR assay with improved synthesis of full-length double-stranded cDNA products in a one-step RT-PCR assay (Gerard, paragraph 12, lines 1-9), with that of Zhao who teaches an aqueous buffer for one-step PCR containing monovalent ions such as potassium glutamate to yield a conductivity in the range of 500 to 20,000 microohms (Zhao, column 6, lines 18-28) for use in a reaction mixture for performing both reverse transcription and PCR in one reaction tube to generate large amounts of amplified DNA from a very small amount of RNA template (Zhao, column 2, lines 7-13 and column 10, lines 50-63). Thus, an ordinary practitioner would have been motivated to combine the methods of Gerard with those of Zhao since Zhao has optimized conditions for performing one-step RT-PCR using buffers containing monovalent ions such as K-glutamate that result in high yields of product from less than 1 ng of RNA template (Zhao, column 10, lines 50-63), while Gerard provides methods for obtaining high yields of full-length products complementary to the original template. Using such methods would allow cDNA products to be readily produced, analyzed, and quantitated for a variety of medical and forensic purposes, or for generating full-length cDNA

molecules to form cDNA libraries from a variety of sources (Gerard, paragraph 12, lines 15-21).

5. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gerard et al. (U.S. Patent Pub. No. 2002/0081581) in view of Zhao et al. (U.S. Patent No. 6,300,073) and further in view of Austin et al. (U.S. Patent No. 5,817,461).

Gerard and Zhao together teach the limitations of claims 20-32 and 34 as discussed above.

Neither Gerard nor Zhao teach a method for amplifying a nucleic acid molecule wherein said buffer further comprises an effective amount of an antifoam compound.

With regard to claim 33, Austin teaches methods of performing polynucleotide enzymatic reactions such as PCR that contain detergents such as Tween, NP-40, and Triton X-100, along with antifoam agents (column 16, line 58 to column 17, line 7).

Austin does not teach methods of combining multiple reverse transcriptases in a one-step RT-PCR assay, such as M-MLV or AMV reverse transcriptases that are reduced in RNase H activity. Austin also does not teach a method for amplifying a nucleic acid molecule under conditions which substantially relieve reverse-transcriptase-mediated inhibition of DNA polymerase activity.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Gerard and Zhao for performing a one-step RT-PCR assay with improved synthesis of full-length cDNA products in a one-step RT-PCR assay (Gerard, paragraph 12, lines 1-9) with high yields

of amplified double-stranded cDNA products from less than 1 ng of RNA using optimized buffer conditions that include the use of glutamate (Zhao, column 6, lines 18-28 and column 10, lines 50-63) with that of Austin who teaches physiological-type conditions for performing amplification reactions such as PCR that often include detergents such as Tween, NP-40, and Triton X-100, along with antifoam agents (Austin, column 16, line 58 to column 17, line 7). Thus, an ordinary practitioner would have been motivated to combine the methods of Gerard and Zhao with those of Austin since performing nucleic acid amplification reactions such as RT-PCR may be improved under more physiological conditions using parameters that are similar to intracellular conditions (Austin, column 16, lines 41-58). Since these may include use of detergents that can cause foaming in reaction tubes or plates that may interfere with analysis or limit product yield, Austin teaches the use of antifoam agents in PCR reactions (column 17, lines 2-7). The use of an antifoam agent may help ensure greater yields of amplified cDNA products that are also similar to or identical in length to the original RNA template. Using such methods would allow cDNA products to be readily produced, analyzed, and quantitated for a variety of medical and forensic purposes, or for generating full-length cDNA molecules to form cDNA libraries from a variety of sources (Gerard, paragraph 12, lines 15-21).

Response to Arguments

6. Applicant's arguments filed February 28, 2007 have been fully considered but they are not persuasive.

Applicant argues that the 35 USC § 102(a) rejection of claims 1-4, 7-12, 18 and 19 under Gerard et al. (U.S. Patent Pub. No. 2002/0081581) should be withdrawn based on cancellation of these claims. Therefore the 102(a) rejection of claims 1-4, 7-12, 18 and 19 over Gerard is withdrawn. In addition, Applicant argues that this reference does not teach every element of the added claims. In particular, Applicant argues that Gerard fails to teach a buffer comprising an amount of glutamate effective to reduce the inhibition of the one or more proteins having DNA polymerase activity. The examiner agrees that Gerard does not teach the use of glutamate in a method of amplifying an RNA template and therefore this reference is also not applied as a 102 rejection of the newly added claims.

However, Zhao teaches methods of obtaining large yields of cDNA product from small amounts of RNA template using a buffer containing glutamate in a one-step RT-PCR assay. Since the methods of Gerard and Zhao are very similar in terms of using reverse transcriptases with reduced RNase H activity in a one-step RT-PCR assay, it is obvious to combine these methods. Since Zhao provides improved buffer conditions using glutamate to obtain an extremely efficient and sensitive amplification method (Zhao, column 10, lines 50-63), there is motivation to combine the methods of Gerard using multiple reverse transcriptase enzymes and those of Zhao. Therefore, newly added claims 20-32 and 34 are rejected under 35 USC § 103(a) over Gerard in view of Zhao.

Applicant then argues that neither Gerard nor Zhao teach or suggest that glutamate ions can be used to reduce the inhibition of DNA polymerase activity in the

presence of one or more reverse transcriptases, but rather that Zhao merely discloses K-glutamate as a convenient source for monovalent cations. Even though Zhao does not explicitly state that glutamate ions reduce the inhibition of DNA polymerase activity in the presence of one or more reverse transcriptases, this reference teaches a method to reduce such inhibition since extremely efficient and sensitive results are obtained using glutamate in the assay buffer. Furthermore, Zhao goes on to state "The subject one step RT-PCR methods find use in any application where the production of enzymatically produced primer extension product from template RNA is desired" (column 10, lines 64-67). Therefore, one of average skill in the art would be motivated to use a method such as that taught by Zhao to obtain large yields of product from less than 1 ng of template RNA, but would not be motivated to use a method wherein polymerase activity would be significantly inhibited, leading to low yield and sensitivity. One of skill in the art would recognize that obtaining yields of up to 1.5 μg from as little as 1 ng (Zhao, column 10, lines 53-57) represents a high product yield and a highly sensitive assay.

Applicant also argues that the method of Zhao for highly efficient one-step RT-PCR used a mutant DNA polymerase instead of one of the wild-type enzymes cited in the instant claims. The mutant DNA polymerases taught by Zhao have reduced nuclease activity, but have full polymerase activity and therefore are useful for primer amplification reactions requiring primer extension (Zhao, column 3, lines 14-21). Furthermore, the polymerases taught by Gerard can be either wild-type enzymes or mutant derivatives (Gerard, paragraph 116, lines 1-11), and therefore the methods for

highly efficient RT-PCR taught by Zhao using a buffer containing glutamate would be highly likely to succeed if combined with the methods of Gerard using two reverse transcriptases and either a wild-type or mutant DNA polymerase.

Finally, Applicant argues that the 35 USC § 103(a) rejection of claim 17 (new claim 33) under Gerard in view of Austin et al. (U.S. Patent No. 6,300,073) should be withdrawn since neither reference, nor in combination with Zhao, teaches all the limitations of the claim. As discussed above, Gerard and Zhao teach all the limitations of claims 20-32 and 34. Since Austin teaches methods of providing an antifoam agent in assays such as PCR, it is obvious to combine these methods with those of Gerard and Zhao for performing one-step RT-PCR and therefore claim 33 is rejected under 35 USC § 103(a) over Gerard in view of Zhao and further in view of Austin.

Summary

7. Claims 20-34 are rejected. No claims are allowable.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David C. Thomas
David C. Thomas 5/4/07
Patent Examiner
Art Unit 1637

JF
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